

Claims

1. Adenovirus expressing a first protein which is selected from the group comprising an E1B protein and an E4 protein, prior to a second protein which is selected from the group comprising an E1A-protein.
2. Adenovirus according to claim 1 characterised in that the first protein is an E1B protein, preferably an E1B55kd protein.
3. Adenovirus according to claim 1, characterised in that the first protein is an E4 protein, preferably an E4orf6 protein.
4. Adenovirus according to any of claims 1 to 3, characterised in that the first protein is a combination of E1B protein and E4 protein, preferably a combination of E1B55kD protein and E4orf6 protein.
5. Adenovirus according to any of claims 1 to 4, characterised in that the E1A protein is an E1A12S protein .
6. Adenovirus, preferably an adenovirus according to any of claims 1 to 5, characterised in that the adenovirus comprises at least one nucleic acid coding for a protein which is selected from the group comprising E1B proteins, E4 proteins and E1A proteins, whereby the at least one protein is under the control of a promoter which is different from the promoter controlling the expression of the protein in a wildtype adenovirus.
7. Adenovirus according to claim 6, characterised in that the at least one protein is an E1B protein, preferably an E1B55kD protein.
8. Adenovirus according to claim 6 or 7, characterised in that the at least one protein is an E4 protein, preferably an E4orf6 protein.
9. Adenovirus according to any of claims 6 to 8, characterised in that the at least one protein is an E1A protein, preferably an E1A12S protein.

10. Adenovirus according to any of claims 6 to 9, characterised in that the at least one protein is a combination of E1B protein and E4 protein, preferably a combination of E1B55kD protein and E4orf6 protein.
11. Adenovirus according to any of claims 6 to 9, characterised in that the at least one protein is a combination of E1B protein and E1A protein, preferably a combination of E1B55kD protein and E1A12S protein.
12. Adenovirus according to any of claims 6 to 9, characterised in that the at least one protein is a combination of E4 protein and E1A protein, preferably a combination of E4orf6 protein and E1A12S protein.
13. Adenovirus according to any of claims 6 to 9, characterised in that the at least one protein is a combination of E1B protein, E4 protein and E1A protein, preferably a combination of E1B55kD protein, E4orf6 protein and E1A12S protein.
14. Adenovirus according to any of claims 6 to 13, characterised in that the expression of the E1B protein is controlled by a promoter, whereby the promoter is selected from the group comprising tumor-specific promoters, organ-specific promoters, tissue-specific promoters, heterologous promoters and adenoviral promoters, whereby the adenoviral promoter is different from the E1B promoter.
15. Adenovirus according to any of claims 6 to 14, characterised in that the expression of the E4 protein is controlled by a promoter, whereby the promoter is selected from the group comprising tumor-specific promoters, organ-specific promoters, tissue-specific promoters, heterologous promoters and adenoviral promoters, whereby the adenoviral promoter is different from the E4 promoter.
16. Adenovirus according to claims 14 or 15, whereby the adenoviral promoter is the E1A promoter.
17. Adenovirus according to any of claims 6 to 16, characterised in that the expression of the E1A protein is controlled by a promoter, whereby the promoter is selected from the group comprising tumor-specific promoters, organ-specific promoters, tissue-specific promoters,

heterologous promoters and adenoviral promoters, whereby the adenoviral promoter is different from the E1A promoter.

18. Adenovirus according to any of claims 14 to 17, characterised in that the promoter controlling the expression of the E1A protein is YB-1 controlled or can be regulated by YB-1.

19. Adenovirus according to any of claims 14 to 18, characterised in that the promoter controlling the expression of the E1A protein is the adenoviral E2 late promoter.

20. Adenovirus according to any of claims 1 to 19, characterised in that the E4 protein, preferably the E4orf6 protein, and the E1B protein, preferably the E1B55kd protein, are under the control of the same or a common promoter.

21. Adenovirus, preferably an adenovirus according to any of claims 1 to 20, characterised in that the adenovirus provides YB-1 in the nucleus through at least one adenoviral protein or that the provision of YB-1 in the nucleus is mediated through at least one adenoviral protein, whereby preferably the adenoviral protein is different from E1A.

22. Adenovirus, preferably according to any of claims 1 to 21, characterised in that the adenovirus provides YB-1 for adenoviral replication through at least one adenoviral protein or mediates the provision of YB-1 for adenoviral replication through at least one adenoviral protein, whereby preferably the adenoviral protein is different from E1A.

23. Adenovirus according to claim 21 or 22, characterised in that the adenoviral protein is a complex of E4orf6 and E1B55kd.

24. Adenovirus, preferably according to any of claims 1 to 23, characterised in that the nucleic acid of the adenovirus comprises at least one functionally inactive adenoviral region, whereby the region is selected from the group comprising the E1 region, the E3 region, the E4 region and combinations thereof.

25. Adenovirus according to claim 24, characterised in that the region is the E1 region.

26. Adenovirus according to claim 24 or 25, characterised in that the region is the E3 region.
27. Adenovirus according to any of claims 24 to 26, characterised in that the region is the E4 region.
28. Adenovirus according to any of claims 24 to 27, characterised in that the region comprises the E1 region, the E3 region and the E4 region.
29. Adenovirus, preferably an adenovirus according to any of claims 1 to 28, characterised in that the adenovirus comprises at least one expression cassette, whereby the expression cassette comprises at least one promoter and a nucleic acid coding for an adenoviral protein, whereby the adenoviral protein is an E1B protein, preferably an E1B55kD protein.
30. Adenovirus according to claim 29, characterised in that the promoter is different from the E1B promoter.
31. Adenovirus according to claim 30, characterised in that the promoter is selected from the group comprising tumor-specific promoters, organ-specific promoters, tissue-specific promoters, heterologous promoters and adenoviral promoters, whereby the promoter is different from the E1B promoter.
32. Adenovirus, preferably according to any of claims 1 to 31, characterised in that the adenovirus comprises at least one expression cassette, whereby the expression cassette comprises at least one promoter and a nucleic acid coding for an adenoviral protein, whereby the adenoviral protein is an E4 protein, preferably an E4orf6 protein.
33. Adenovirus according to claim 32, characterised in that the promoter is different from the E4 promoter.
34. Adenovirus according to claim 33, characterised in that the promoter is selected from the group comprising tumor-specific promoters, organ-specific promoters, tissue-specific promoters, heterologous promoters and adenoviral promoters, whereby the adenoviral promoters are different from the E4 promoter.

35. Adenovirus according to any of claims 29 to 34, characterised in that the promoter is the E1A promoter.
36. Adenovirus, preferably according to any of claims 1 to 35, characterised in that the adenovirus comprises at least one expression cassette, whereby the expression cassette comprises at least one promoter and a nucleic acid coding for an adenoviral protein, whereby the adenoviral protein is an E1A protein, preferably an E1A12S protein.
37. Adenovirus according to claim 36, characterised in that the promoter is different from the E1A promoter.
38. Adenovirus according to claim 37, characterised in that the promoter is selected from the group comprising tumour-specific promoters, organ-specific promoters, tissue-specific promoters, heterologous promoters and adenoviral promoters.
39. Adenovirus according to any of claims 1 to 38, characterised in that the adenovirus comprises a nucleic acid, whereby the nucleic acid codes for YB-1.
40. Adenovirus according to claim 39, characterised in that the nucleic acid coding for YB-1 is under the control of a promoter, whereby the promoter is preferably the E2 late promoter.
41. Adenovirus according to claim 39 or 40, characterised in that the nucleic acid coding for YB-1 is under the control of a promoter, whereby the promoter is YB-1 dependent and YB-1 controlled, respectively.
42. Adenovirus according to any of claims 35 to 41, characterised in that the nucleic acid coding for YB-1 is part of the expression cassette comprising a nucleic acid coding for an E1A protein, preferably a nucleic acid coding for an E1A12S protein.
43. Adenovirus according to claim 42, characterised in that the nucleic acid coding for the E1A protein is separated from the nucleic acid coding for YB-1 through an IRES sequence.

44. Adenovirus according to any of claims 29 to 43, characterised in that the nucleic acid coding for the E4 protein, preferably the E4orf6 protein, and the nucleic acid coding for the E1B protein, preferably the E1B55kD protein, are contained in an expression cassette, whereby preferably the two coding sequences are separated through an IRES sequence.
45. Adenovirus according to claim 44, characterised in that the promoter of the expression cassette is selected from the group comprising tumor-specific promoters, organ-specific promoters, tissue-specific promoters, heterologous promoters and adenoviral promoters, whereby the adenoviral promoters are different from the E4 promoter and different from the E1B promoter, preferably different from the wildtype E4 promoter and different from the wildtype E1B promoter.
46. Adenovirus according to any of claims 1 to 45, characterised in that the adenovirus comprises an expression cassette comprising a promoter and a nucleic acid sequence, whereby the nucleic acid sequence is selected from the group comprising aptamers, ribozymes, aptazymes, antisense molecules and siRNA.
47. Adenovirus according to any of claims 1 to 45, characterised in that the adenovirus comprises an expression cassette comprising a promoter and a nucleic acid sequence, whereby the nucleic acid sequence is a coding nucleic acid, whereby the nucleic acid codes for a molecule which is selected from the group comprising peptides, polypeptides, proteins, anticalines, antibodies and antibody fragments.
48. Adenovirus according to any of claims 1 to 45, characterised in that the adenovirus comprises an expression cassette, whereby the expression cassette comprises a promoter and a nucleic acid sequence, whereby the nucleic acid sequence is selected from the group comprising apoptosis inducing genes, prodrug genes, protease inhibitors, tumor suppressor genes, cytokines and angiogenesis inhibitors.
49. Adenovirus according to any of claims 1 to 48, characterised in that the adenovirus is a recombinant adenovirus.
50. Adenovirus according to any of claims 1 to 49, characterised in that the adenovirus is an adenovirus mutant.

51. Adenovirus according to any of claims 1 to 50, characterised in that the adenovirus is replication deficient.
52. Adenovirus according to claim 51, characterised in that the adenovirus is capable of replicating in cells comprising deregulated YB-1 or having YB-1 in the nucleus.
53. Adenovirus according to claim 52, characterised in that the cells contain YB-1 in the nucleus independent of the cell cycle.
54. Nucleic acid coding for an adenovirus according to any of claims 1 to 53.
55. Replication system comprising a nucleic acid according to claim 54 and a nucleic acid of a helper virus, whereby the nucleic acid of the helper virus comprises one or more of the expression cassettes of the adenovirus according to any of claims 1 to 53.
56. Replication system according to claim 55, characterised in that the adenovirus or the nucleic acid coding therefor is lacking the expression cassette comprised by the helper virus.
57. Vector comprising a nucleic acid according to claim 54 and/or a replication system according to any of claims 55 to 56.
58. Vector according to claim 57, characterised in that the vector is an expression vector.
59. Cell comprising an adenovirus according to any of claims 1 to 53 and/or a nucleic acid according to claim 54 and/or a replication system according to claim 55 or 56 and/or a vector according to claim 57 or 58.
60. Cell according to claim 59, characterised in that the cell is a eucaryotic cell, preferably an animal cell, more preferably a mammalian cell.
61. Cell according to claim 60, characterised in that the mammalian cell is a cell selected from the group comprising cells of mice, rats, guinea pigs, pigs, sheep, goats, cattle, horses, dogs, cats and human beings.

62. Organism, preferably a mammal organism, comprising an adenovirus according to any of claims 1 to 53, a nucleic acid according to claim 54, a replication system according to claim 55 or 56, a vector according to any of claims 57 or 58 or a cell according to any of claims 59 to 61, whereby the organism is preferably selected from the group comprising mice, rats, guinea pigs, pigs, sheep, goats, cattle, horses, dogs and cats.

63. Use of an adenovirus according to any of claims 1 to 53, a nucleic acid according to claim 54, a replication system according to claim 55 or 56, a vector according to any of claims 57 or 58, or a cell according to any of claims 59 to 61, for replication of an adenovirus, preferably for in vitro replication of an adenovirus.

64. Use of an adenovirus according to any of claims 1 to 53, a nucleic acid according to claim 54, a replication system according to claim 55 or 56, a vector according to any of claims 57 or 58, or a cell according to any of claims 59 to 61 for the manufacture of an adenovirus, preferably for in vitro manufacture of an adenovirus.

65. Use of an adenovirus according to any of claims 1 to 53, a nucleic acid according to claim 54, a replication system according to claim 55 or 56, a vector according to any of claims 57 or 58, or a cell according to any of claims 59 to 61 for the expression of genes, preferably of genes which promote cell lysis, preferably cell lysis during adenoviral replication, and/or are promoting adenoviral mediated cell lysis.

66. Use of an adenovirus according to any of claims 1 to 53, a nucleic acid according to claim 54, a replication system according to claim 55 or 56, a vector according to any of claims 57 or 58, or a cell according to any of claims 59 to 61 for the manufacture of a medicament.

67. Use according to any of claims 63 to 66, characterised in that the cell in which the adenovirus replicates, has YB-1 in its nucleus, preferably has YB-1 in its nucleus independent of the cell cycle.

68. Use according to any of claims 63 to 66, characterised in that the cell in which the adenovirus replicates, comprises deregulated YB-1.

69. Use according to claim 66, characterised in that the medicament is for the treatment of tumor diseases.
70. Use according to claim 69, characterised in that the tumor disease is selected from the group comprising malignant diseases, cancer, cancer diseases and tumors.
71. Use according to claim 70, characterised in that the tumors are selected from the group comprising solid, non-solid, malignant and benign tumors.
72. Use according to any of claims 69 to 71, characterised in that at least one part of the tumor forming cells have YB-1 in the nucleus, preferably have YB-1 in the nucleus independent of the cell cycle.
73. Use according to any of claims 69 to 72, characterised in that at least a part of the cells forming the tumor comprises deregulated YB-1.
74. Use according to any of claims 69 to 73, characterised in that at least a part of the cells forming the tumor are Rb positive or Rb negative.
75. Use according to any of claims 69 to 73, characterised in that at least a part of the cells forming the tumor have a resistance, preferably a multiple resistance against pharmaceutically active agents.
76. Use according to claim 75, characterised in that the resistance is a multiple resistance.
77. Use according to any of claims 75 or 76, characterised in that the resistance is against anti-tumor agents, preferably cytostatics, and/or that the resistance is caused by irradiation.
77. Use according to any of claims 69 to 76, characterised in that the patient for which the medicament is intended, comprises a plurality of cells, whereby the cells are cells as described in any of claims 72 to 76.
78. Use according to any of claims 69 to 77, characterised in that the medicament comprises at least one further pharmaceutically active agent.

79. Use according to any of claims 68 to 77, characterised in that the medicament is administered together with a further pharmaceutically active agent or is intended therefor.

80. Use according to claim 78 or 79, characterised in that the further pharmaceutically active agent is selected from the group comprising cytokines, metalloproteinase inhibitors, angiogenesis inhibitors, cytostatics, tyrosine kinase inhibitors, cell cycle inhibitors, proteasome inhibitors, inhibitors of the signal transduction cascade, protein kinases and recombinant antibodies.

81. Use according to any of claims 69 to 77, characterised in that the medicament is administered prior, during or after irradiation.

82. Use according to claim 81, characterised in that the radiation is administered for the purpose of treating a tumor.

83. Use according to any of claims 69 to 82, characterised in that the cell or the organism to be treated is subject to a measure, whereby the measure is selected from the group comprising irradiation, administration of cytostatics and hyperthermia.

84. Use according to any of claims 69 to 83, characterised in that the measure is applied locally or systemically.

85. Use according to any of the preceding claims, characterised in that the irradiation uses high-energy radiation, preferably uses any irradiation as used in the treatment of tumor diseases.

86. Use of an adenovirus according to any of claims 1 to 53, a nucleic acid according to claim 54, a replication system according to claim 55 or 56, a vector according to any of claims 57 or 58, or a cell according to any of claims 59 to 61 for the manufacture of a medicament for the treatment of tumor diseases, characterised in that the tumor disease is selected from the group comprising breast tumors, bone tumors, gastric tumors, intestinal tumors, gall-bladder tumors, pancreas tumors, liver tumors, kidney tumors, brain tumors, ovarian tumors, skin tumors, tumors of cutaneous appendages, head and neck cancer, uterine tumors, synovial

tumors, laryngeal tumors, oesophageal tumors, lingual tumors, prostate tumors, preferably one of the preceding tumor diseases having the characteristics as described in any of the preceding claims.

87. Use of an adenovirus according to any of claims 1 to 53, a nucleic acid according to claim 54, a replication system according to claim 55 or 56, a vector according to any of claims 57 or 58, or a cell according to any of claims 59 to 61 for the manufacture of medicament for the treatment of tumor diseases, whereby the tumor-specific promoter is a promoter which is specific for the tumor for which the medicament is used.

88. Pharmaceutical composition comprising an adenovirus according to any of claims 1 to 53, a nucleic acid according to claim 54, a replication system according to claim 55 or 56, a vector according to any of claims 57 or 58, or a cell according to any of claims 59 to 61 and optionally a pharmaceutically acceptable carrier.

89. Use according to any of the preceding claims, characterised in that the medicament comprises a combination of at least two agents, whereby each agent is individually and independently selected from the group comprising cytostatics.

90. Use according to claim 89, characterized in that at least two of the agents address different target molecules.

91. Use according to claim 90, characterized in that at least two of the agents are active by a different mode of action.

92. Use according to any of claims 89 to 91, characterized in that at least one agent increases the ability of a cell to be infected, whereby the virus replicates in such cell.

93. Use according to any of claims 89 to 92, characterized in that at least one agent influences the availability of a component of the cell, preferably increases the availability of the component, whereby the component mediates the uptake of the virus.

94. Use according to any of claims 89 to 93, characterized in that at least one agent mediates the transport of YB-1 into the nucleus, preferably increases said transport.

95. Use according to any of claims 89 to 94, characterized in that at least one agent is a histone deacetylase inhibitor.
96. Use according to claim 95, characterized in that the histone deacetylase inhibitor is selected from the group comprising Trichostatin A, FR 901228, MS-27-275, NVP-LAQ824, PXD101, Apicidin and Scriptaid.
97. Use according to any of claims 89 to 95, characterized in that at least one agent is selected from the group comprising Trichostatin A, FR 901228, MS-27-275, NVP-LAQ824, PXD101, Apicidin and Scriptaid.
98. Use according to any of claims 89 to 97, characterized in that at least one agent is a topoisomerase inhibitor.
99. Use according to claims 98, characterized in that the topoisomerase inhibitor is selected from the group comprising Camptothecin, Irinotecan, Topotecan, DX-8951f, SN-38, 9-aminocamptothecin, 9-nitrocamptothecin, Daunorubicin and Etoposide.
100. Use according to any of the preceding claims, characterized in that the agent comprises Trichostatin A and Irinotecan.
101. Use according to any of the preceding claims, characterized in that the virus, in particular the virus according to any of the preceding claims, is separated from the at least two agents.
102. Use according to claim 68, characterized in that at least one unit dose of the virus is separated from at least one unit dose of one or the at least two agents.
103. Kit comprising a virus, preferably a virus according to any of the preceding claims, and at least two agents, whereby any agent is individually and independently selected from the group comprising cytostatics.